UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,815	02/18/2005	Erich Gulbins	26610U	1995

20529 7590 07/09/2008

NATH & ASSOCIATES
112 South West Street
Alexandria, VA 22314

EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ip@nathlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/524,815	GULBINS, ERICH	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Office Action is in response to the amendment submitted on 03/31/08. Newly added claims 37-39 are currently pending in the application, with claims 1-36 having being cancelled. Accordingly, claims 37-39 are being examined on the merits herein.

Claims 20, 22, 24, 33, and 35-36 were rejected under 35 U.S.C. § 112, second paragraph due to presence of the indefinite terms "in particular" in the aforementioned claims. However, given the cancellation of the aforementioned claims, the rejection is withdrawn.

Claim 23 was objected to because of a typographical error. However, given the cancellation of the aforementioned claim, the objection is now withdrawn.

Claims 19-32 were rejected under 35 U.S.C. § 101 for not reciting any step (s) in a method/process claim. However, in light of the cancellation of the aforementioned claims, the rejection of claims 19-32 is now withdrawn.

Claims 19-36 were rejected under 35 U.S.C. § 112, first paragraph for not enabling the prophylaxis treatment of infectious diseases or diseases influenced by

infection or making the pharmaceutical compositions as claimed. However, in light of the cancellation of the aforementioned claims, the rejection of claims 19-36 is now withdrawn.

Claims 19-32 were rejected under 35 U.S.C. § 112, second paragraph due to the lack of clarity as to what the method actually encompass. However, given the cancellation of the aforementioned claims, the rejection is now withdrawn.

Claims 19, 24, 26-30, and 34-36 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Grassme et al.. However, in view of the cancellation of the aforementioned claims, the rejection is now withdrawn.

Claims 19-22, 27, 29, and 33 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Hauck et al. However, in view of the cancellation of the aforementioned claims, the rejection is now withdrawn.

Claims 19-22, 27, 29, and 33 were rejected under 35 U.S.C. § 103 (a) as being obvious over Grassme in view of Hauck and in further view of Claus et al. and Haimovitz-Friedman et al. However, in view of the cancellation of the aforementioned claims, the rejection of claims 19-22, 27, 29, and 33 i under 35 U.S.C. § 103 (a) s now withdrawn.

Applicant's argument with respect to claims 37-39 as being patentable under 35 U.S.C. § 101, clear and definite within the meaning of 35 U.S.C. § 112, second

paragraph, fully enabled by the specification within the meaning of 35 U.S.C. § 112, first paragraph, and as being non-anticipated and non-obvious over Grassme, Hauck, Claus, and Haimovitz-Friedman et al. has been considered but is not found persuasive. In fact, such arguments are moot given that the newly presented claims are yet to be searched for determination of patentability. Thus, applicant's arguments with respect to claims 37-39 have been considered but are moot in view of the new ground(s) of rejection.

For the foregoing reasons and in light of their cancellations, the rejection of claims 1-36 is withdrawn. However, in view of applicant's addition the following 103 (a) Final rejection is being made.

Objection to the Specification --- 35 USC 132(a)

1. The substitute specification filed 03/31/08 is objected to because it does not conform to 37 CFR 1.125(b) and (c) because: it contains new matter and is in improper form. A substitute specification submitted under this section must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings)

must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown pursuant to this paragraph. As a result, the amendment filed 03/31/08 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Entire specification and drawings.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cystic fibrosis, does not reasonably provide enablement for a method of prophylaxis (i.e. prevention) treatment of cystic fibrosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Importantly, given that the term “prevention” implies an absolute term, it is assumed that no known disease can be absolutely prevented at this time or completely hindered. For example, applicant does not reasonably provide enablement for the prophylaxis treatment of cystic fibrosis in the specification filed on

02/18/05. Rather applicant suggests on pg. 19 of the specification that the treatment of mice infected with P. aeruginosa, a bacterial infection often detected in cystic fibrosis, can benefit by targeting the enzyme acid sphingomyelinase. Additionally, given the unpredictability of the treatment of cystic fibrosis, the application does not enable any person skilled in the art to use the invention to prevent cystic fibrosis.

The instant claims are drawn to a method of prophylaxis or treatment of cystic fibrosis comprising administering a tricyclic or tetracyclic antidepressant or substances derived from tricyclic or tetracyclic antidepressant. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention as claimed.

Attention is directed to *In reWands,* 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. <u>The nature of the invention, state and predictability of the art, and relative skill level</u>

The invention relates to a method a method of prophylaxis or treatment of cystic

fibrosis comprising administering a tricyclic or tetracyclic antidepressant or substances derived from tricyclic or tetracyclic antidepressant. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites the fact that cystic fibrosis is a hereditary disease causes by genetic abnormalities and as such cannot be absolutely prevented.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prevention" as "to keep from happening or existing", i.e., to completely eradicate.

The claims are thus very broad insofar as they recite the "prevention" of cystic fibrosis, i.e., the complete eradication of same. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live as hereditary abnormalities cannot be absolutely in patients who already possess the genetic abnormalities.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for a method for preventing

cystic fibrosis by administering a tricyclic or tetracyclic antidepressant or substances derived from tricyclic or tetracyclic antidepressant. In fact, applicant only provided guidance for treatments of cells infected with a virus or bacterium with amitriptyline (see fig 4, specification filed on 02/18/05.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant could be predictably used to prevent cystic fibrosis as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation in order to determine if said tricyclic or tetracyclic antidepressant or substances derived therefrom can prevent or forever hinder the appearance of cystic fibrosis, with no assurance of success.

Genentech, 108 F.3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

5. Suggested alternative language

Since the term "treating" is inclusive of various administrative timing schemes and thus provides adequate coverage for all reasonably successful therapies (prophylactic or active), the examiner recommends deleting the term "prophylaxis" and simply reciting "treating" instead.

Therefore, a method for prophylaxis of prophylaxis of cystic fibrosis comprising administering a tricyclic or tetracyclic antidepressant or substances derived from tricyclic or tetracyclic antidepressant is not considered to be enabled by the instant specification.

The claims are examined herein for a method of treating cystic fibrosis comprising administering a tricyclic or tetracyclic antidepressant or substances derived from tricyclic or tetracyclic antidepressant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-39 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Grassme et al. (Nature Medicine, March 2003, Vol. 9, No. 3, pgs. 322-330) in view of Albouz et al. (Neuro. Sci. Letters, 1983, Vo. 36, pg. 311-315, already cited by applicant and filed on an IDS 1449).

Grassme et al. teaches P.aeruginosa is one of the most severe infection that affects patients with cystic fibrosis (see Introduction, pg. 322, left col., paragraph 1). In fact, recurrent infection of P. aeruginosa often leads to pneumonia, a primary cause of lung destruction in patients with cystic fibrosis (see Introduction, pg. 322, left col., paragraph 1). Grassme also teaches that sphingolipid-enriched platforms (i.e. rafts), signaling-induced platforms, are induced by the bacterium P. aeruginosa (see pg. 322, Introduction, left col.). It does so by inducing clustering the cystic fibrosis transmembrane conductance regulator molecule (i.e. CFTR) implicated in P. aeruginosa internalization and through the induction of apoptosis in the bronchi detected through *in vivo* analysis (see pg. 323 and pg. 324, left col.). Moreover, Grassme determined that modulation of the signaling platforms led to the release of pro-inflammatory cytokines after infection with P. aeruginosa (see pg. 324, right col.). Additionally, the study of Grassme demonstrated that infection by P. aeruginosa activates Acid sphingomyelinase (i.e. ASM), translocates it to the extracellular leaflets of cells in the bacteria containing-raft platforms and release ceramide in an non-tissue specific manner (i.e. same observation in all tissues suggesting the same mechanism is operating in the lungs of cystic fibrosis patients; see pg. 325-236). Grassme et al. further suggests that infection

with P. aeruginosa triggers ASM surface translocation where its activation causes release of deleterious cytokines such as IL-1 and imbalance of ceramide, an apoptosis inducing molecule (see pg. 327, left col.) along with internalization of the bacterium into the host cell which consequently leads to pneumonia and eventual death in mice models(see pg. 327). In summary, Grassme et al. teaches that modification of sphingolipid-rich rafts and generation of larger platforms due to activation of ASM-induced release of ceramide play a role in the defense against P. aeruginosa infection (see pg. 328, right col.). The study of Grassme et al. suggests that targeting molecules that modulates signaling platforms (i.e. ASM) should provide novel therapeutic treatment against P.aeruginosa, an infection found in cystic fibrosis.

Grassme et al. does not teach therapeutic compounds for the treatment of cystic fibrosis.

Albouz et al. teaches the use of tricyclic antidepressants in decreasing ASM activity (see abstract). Importantly, Albouz et al. teaches that both the tricyclic antidepressants imipramine and desimipramine (instant claims 38-39) are effective in drastically reducing ASM in cultured fibroblasts (see pg. 312, paragraph 1). Albouz et al. further tested other cells (i.e. other cells in other tissues) including glioma cells (i.e. brain cells) in the presence of both imipramine and desimipramine and found a reduction in sphingomyelinase activity in a dose-dependent, time-dependent, non-tissue specific manner(pgs. 312, last paragraph, 314, top paragraph, and see tables 1-2). Importantly, Albouz et al. suggests that the concentration used for the observed

reduction mimics dosage that can modified membrane fluidity physiologically; this suggests *in vivo* application (see pg. 314, last paragraph).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the tricyclic depressants of Albouz et al. to inactivate ASM since Grassme et al. teaches that ASM activation leads to modulation of signaling and internalization of P.aeruginosa, the bacterium involved in cystic fibrosis. Given that Grassme et al. teaches that ASM activation leads to modulation of signaling, internalization of P.aeruginosa, and pneumonia in cystic fibrosis patients, and Albouz et al. teaches tricyclic antidepressants capable of decreasing ASM activity, one of ordinary skill in the art would have been motivated to utilize imipramine and desimipramine in the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and pneumonia-induced by P. aeruginosa.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

07/01/2008

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617